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Everett Naughtin Collins, M.D.

Staff Member, The Cleveland Clinic Foundation, 1931—
Department of Radiology 1931—1936
Head, Department of Gastroenterology 1936—

Born October 25, 1896
Died November 6, 1959

Everett Naughtin Collins, M.D.

ED COLLINS died in his sleep during the early morning hours of November 6, 1959. Born on a farm near Ganges, Michigan, in the horse-and-buggy days, Ed was the son of a long line of farmers, and the first physician in the family. His ambition to be a physician arose in childhood and was born of his admiration for the family physician of Ganges, Doctor Brunson. The intensity of Ed's desire to become a doctor was at first not recognized by his family, but it never waned.

He was a self-made man. After graduation from Benton Harbor High School he "worked his way" through Kalamazoo College and The University of Chicago Medical School. Ed was outstanding wherever he was or whatever project he attempted. At Kalamazoo College he was the state champion high jumper, and president of his senior class. The money that paid his way through college and medical school was earned in a variety of ways, such as stoking the furnace in the local church, door-to-door selling of "Keystone Stereoscopic Viewers," being fireman on a train, playing the piano in night clubs.

He met the girl who was to become his wife, the former Dorothy Tempest, at a Christmas party in Edmonton, Alberta, Canada, in 1920. At that time, Ed had had to stop attending medical school in Chicago for want of money. Partly because he had been an A student in anatomy and partly through the help of Dr. R. R. Bensley, then Chairman of the Department of Anatomy of The University of Chicago, he obtained a position as instructor in anatomy at the University of Alberta. Ed and Dorothy were married in September of 1922, and Ed used to like to tell of the honeymoon trip in a model-T Ford with a tent, and of the difficulties in the deluge of rain that first night after their marriage.

Dorothy was a social worker in the slums of Chicago while Ed finished his medical training; he intended to become a surgeon, as he found himself greatly influenced by his teacher, Dr. Dean Lewis. However, this ambition was postponed for one more year in order to work with Dr. Bertram W. Sippy. Ed and Dorothy then moved to Aurora, Illinois, with the intention that Ed would practice surgery at the Brennecke Clinic. The need for expert roentgenology was great and his efforts were soon diverted to spending nearly all of his time with gastrointestinal roentgen diagnosis, and for a year or more he continued his postgraduate studies by traveling once or twice each week to attend lectures in Chicago.

Today, physicians specially trained in gastrointestinal radiology, and particularly with a good training in medical gastroenterology are not plentiful—they were much more of a rarity then, and Ed was a pioneer in his field. It was through his experience and continued study that he acquired the distinction of becoming certified as a specialist in two branches of medicine, the first, Internal Medicine in the subspecialty of Gastroenterology, and the second, Radiology.

Dr. Bernard H. Nichols, who was for many years Head of the Department of Radiology here at the Cleveland Clinic, met Doctor Collins in Aurora after Ed

had seven years of experience. Doctor Nichols was impressed by the excellence of the training of this young physician, with his intelligence, friendliness, and enthusiasm. Eager for still more training, Ed joined the Staff of the Cleveland Clinic in 1931, primarily with the idea of becoming a more skillful expert in gastrointestinal radiology.

The extraordinarily high quality of his roentgen diagnoses was recognized immediately by the Clinic Staff, but they were even more impressed by his medical opinions with regard to clinical diagnosis and treatment. As time went on, Ed found himself spending so much of his own time advising other Staff members about difficult problems in gastroenterology it was decided that he should officially be a consultant in that field. The Department of Gastroenterology was formed in 1936, actually by popular demand, with Doctor Collins as Head.

His enthusiasm in his chosen field in medicine never waned, and it is doubtful that anyone on our Staff can remember a single instance in which Ed found it impossible to see a sick person when he was asked to do so. His work was always marked by thoughtful and meticulous care; no detail was too small to receive his careful attention, and for these reasons his opinion was highly respected. His patients, also, soon sensed his deep concern with their problems, and they could see clearly the evidence of kindliness and human warmth that made him trusted and beloved.

His devotion to his wife and family was constant, and his generosity to his mother and father, his concern for the welfare of his daughter, Joan Engstrom, the support of the long medical training of his son, Dr. Jack Collins, and of his architect son, Bill, were magnificent.

Ed will continue to live in the memories of his friends, his students, his associates in our group and nationally, and particularly in the minds and the memories of his family, and of the thousands of patients whom he helped.

E. PERRY MCCULLAGH, M.D.

VASCULAR NECK PAIN—A COMMON SYNDROME SELDOM RECOGNIZED

Analysis of 100 Consecutive Cases

LEONARD L. LOVSHIN, M.D.
Department of Internal Medicine

A YOUNG or middle-aged woman reports to her physician because of a sore throat, without fever or other constitutional manifestations, which may have been present for weeks or months. The patient believes that the glands in the neck are swollen. These "swollen glands" are said to act strangely: sometimes the swelling lasts only a few hours, sometimes it persists for weeks; it disappears mysteriously and recurs frequently. During the course of the physical examination the physician finds no abnormality, but when he re-examines the neck and follows the directions given by the patient, he finds a tender swelling that *could* be an inflamed lymph node.

The patient then is treated with a sulfonamide or with penicillin, and, when no relief ensues, a course of one of the broad-spectrum antibiotics is administered. This therapeutic program also is unsuccessful, and the harried physician begins to think of other possibilities. Since the patient has "swollen glands," feels weak, tired, and run-down, and antimicrobial therapy has not helped, a diagnosis of infectious mononucleosis may be considered. But, results of a heterophil antibody test are negative, and the diagnosis is changed to possible viral infection.

After several weeks or months of having diagnoses changed, the nervous patient can sense that her physician is uncertain, and she begins to worry about the looming possibility of cancer. She keeps poking in the region of the soreness, and the area becomes even more tender. In desperation, further investigations are carried out and nothing definitely abnormal is found. Teeth are removed or the tonsils are excised; and sometimes the pain disappears for a while, only to return and persist for days or weeks. Occasionally the thyroid gland is suspect, and a diagnosis of subacute thyroiditis is made; however, treatment with roentgen rays or steroids gives no relief.

This patient has vascular neck pain, a condition analogous to extracranial vascular headache. The syndrome of vascular neck pain is not due to structural change; it is benign and reversible; it is as real as migraine headache. There is no inflammation or adenopathy. What is so often described as a swollen gland is merely a tender, distended segment of the carotid artery. This distention is a manifestation of dysfunction of the autonomic nervous system, and is closely related to the painful vasodilating syndromes of the face and the head. Physicians are well aware of the nuchal radiation that occurs during an attack of migraine, when pain commonly radiates to the anterior portion of the neck, and tenderness develops in the carotid area. It is when the vascular neck pain occurs without headache that there is so much diagnostic difficulty.

Watson and Thorn[1] in 1952 listed 43 causes of neck pain, and discussed the differential diagnosis in considerable detail. They recognized only organic conditions, many of them rare, and did not mention the extremely common functional neck pains of carotid or muscular origin. Fay[2] coined the term "carotidynia" in 1927, but he used it in describing the tenderness of the carotid artery in association with particular forms of atypical facial neuralgia. Hilger,[3] in 1949, in discussing the general aspects of carotid pain, apparently first described the syndrome of vascular neck pain: "The patient usually complains of the recurrent and abrupt onset of unilateral sore throat with the appearance of a 'gland' in the neck. There is no evidence of inflammation. The bifurcation is palpable as a firm, extremely tender mass at the hyoid level. It pulsates—an important diagnostic point. Usually the tonsils have been removed in previous efforts to alleviate the recurrences of sore throat." Unfortunately, little attention has been paid to this succinct paragraph, and the syndrome of carotid neck pain remains unrecognized generally.

Wolff[4] has stressed the interrelationship of the various vascular pains in the head, and considers the underlying mechanisms to be the same in each clinical pattern. Thus, a vasodilating hemicrania preceded by visual scotomata and associated with nausea and vomiting is called migraine. A vasodilating headache without all of the typical characteristics of migraine may be called atypical migraine or tension vascular headache. The vascular headache occurring with hypertension, but not directly related to it, is another variant. Histaminic cephalalgia, described by Horton, MacLean, and Craig[5] in 1939, was thought to be a unique form of vascular headache related to hypersensitivity to histamine, or to an overproduction of histamine; they outlined a method of treatment based on desensitization to histamine. After extensive clinical trials, most observers have concluded that such desensitization is not a specific therapy for histaminic cephalalgia. This headache is now commonly regarded as a variant of migraine. For many years there has been confusion in the classification of atypical facial pain—and the syndromes of atypical facial neuralgia, sphenopalatine ganglion neuralgia, and vidian neuralgia were described. There is considerable evidence that all of these are vascular pains of the face, in which there is involvement of the facial branches of the external carotid artery, chiefly of the maxillary branch. When the distention and relaxation affect the carotid trunk alone, the syndrome of vascular neck pain results.

Clinical Characteristics

Vascular neck pain has been observed in children as young as 10 years and in adults as old as 75 years of age. It occurs more commonly in females than in males, the ratio being about 4 to 1. A carefully taken family history almost always indicates that one of the grandparents, parents, or siblings has suffered from one of the vascular syndromes. The patient's history is significant; many times migraine or other vascular headaches have occurred. Headache may have alternated with the bouts of neck pain, but usually the headaches become less frequent after the neck pain develops.

Usually the patient's temperament is similar to that commonly described for the person who suffers from migraine, namely, sensitive, conscientious, and perfectionistic. He is likely to be rigid, reserved, and strives to be well thought of. The neck pain may occur in a setting of fatigue, frustration, or tension; but also it may occur, as does migraine, with relaxation after a period of stress. A week-end neckache is just as diagnostic of vascular neck pain as a week-end headache is of vascular headache. The neckache is dull and feels deep-seated, and usually is not throbbing, but a throbbing component can be evoked by stooping, bending, or straining.

The discomfort is difficult to locate exactly, and though it often is described as being a sore throat, close questioning will elicit the fact that basically it is a sore neck. The thyroid gland is not tender. Usually the pain is centered about the carotid bulb and radiates upward along the course of the external carotid artery, behind the mandible, and up into the postauricular area. At times, the patient has a mild earache on the affected side. Most often the pain is unilateral, but it may move from one carotid area to the other and become bilateral. The pain in the region of the carotid artery is similar to that produced in cervical adenitis, so that confusion in diagnosis often occurs.

Usually the pain is not severe and it does not strike with the force noted in some types of vascular headache. There may be mild nausea but no vomiting. In general, the duration is longer than that of vascular headache; an almost continuous aching for from two to eight weeks is usual. The pain engenders a considerable emotional reaction. Since many of the patients with vascular neckache have a worrisome nature and are rather sensitive, they intuitively know when the physician is groping for a diagnosis and an effective method of treatment. Their intuitions give rise to more apprehension and worry; often cancerophobia develops.

Physical Findings

The findings on physical examination are normal except for the presence of a tender, throbbing carotid artery on the painful side. The tenderness is greatest at the carotid bifurcation or under the mandible. Of particular significance is the absence of injection of the pharyngeal mucous membrane; the tonsils are not inflamed; and there is no exudate. Adenitis is absent. The sternocleidomastoid muscle often is tender. This tenderness most likely is due to reflex muscle spasm. A tender carotid artery is easily demonstrated by pressing it posteriorly against the transverse processes of the cervical vertebrae and rolling the vessel under the fingers. All carotid arteries are somewhat tender, but these affected arteries are unduly so. The dilatation may be extreme, and at times may suggest a diagnosis of carotid aneurysm or carotid body tumor.

Often there are other evidences of dysfunction of the autonomic nervous system. Motion sickness and vertigo are more prevalent in persons afflicted with vascular pain than in the general population.

Analysis of a Series of 100 Cases

The Cleveland Clinic records of 100 consecutive patients with diagnoses of vascular neck pain (1954 through 1956) were analyzed. There were 82 females and 18 males; 62 patients had a history of previous vascular headache; 45 patients volunteered the information that the glands in the neck had been swollen. At the time of the examination, 73 of the 100 patients had tenderness of one or of both carotid arteries. The 27 who did not have demonstrable tenderness were not having vascular neck pain at the time of examination.

Age. The age range of the 100 patients was from 10 to 79 years; most of the patients were in the fifth decade of life. The age distribution of the 100 patients was: 10 to 19 years (1 patient), 20 to 29 years (17 patients), 30 to 39 years (21 patients), 40 to 49 years (31 patients), 50 to 59 years (19 patients), 60 to 69 years (9 patients), 70 to 79 years (2 patients).

Previous diagnoses. Although more than half of the patients had sought previous medical care, in no case had the correct diagnosis been made. Eleven patients had been told the neck pain was due to tonsillitis or infected throat. For six patients, the pain had been thought to result from carotid tumor or aneurysm, and three of those patients were referred for consideration of vascular surgery. Six patients were told they had thyroid disease, four of whom were referred directly to a thyroid surgeon. Infectious mononucleosis was the diagnosis for two patients. The others were given no definite diagnosis, or could not recall what they had been told.

Previous therapy. Courses of antibiotics had been given to 13 patients; 9 had dental extractions; 2 underwent subtotal thyroidectomy; 2 received a course of cortisone; and 1 patient had the jawbone scraped. Since the patients were still having neck pains, it can be assumed that treatment was not successful.

Treatment

Basically, the treatment for vascular neck pain is the same as the treatment for the other painful vasodilating syndromes of the head. Since the severity of the pain is less than in migraine or histaminic cephalalgia, and since the underlying neurosis (if any) is milder than that occurring in patients with vascular facial pain, the result of treatment of vascular neck pain is more satisfactory than that of migraine, histaminic cephalalgia, or vascular facial pain.

Because pain is a subjective phenomenon, and the occurrence of vascular pain is periodic and unpredictable, it is difficult to evaluate the result of a particular therapeutic agent in this group of conditions. The best therapists are enthusiasts; however, it is this same enthusiasm that when expressed in medical writing, often results in uncritical evaluation. The fact that more than 400 ways of "curing" vascular headache have been reported in the medical literature, indicates that no really successful therapy has been discovered. The study of any specific treatment undertaken without proper control, and evaluated without careful follow-up of at least two years' duration would only add to the confusion.

The following discussion of treatment used in the 100 cases of vascular neck pain offers no new therapeutic agent, but it summarizes a satisfactory program for handling the problem.

Psychologic treatment. Treatment begins with a painstakingly careful physical examination. Consultations must be obtained when necessary, but the diagnosis is made by utilizing positive evidence and not merely by the elimination of the possibility of organic disease. In a benign condition such as vascular neck pain, especially when the pain is not severe, reassurance is sometimes all that is needed. Many patients seek medical aid not because of the aching neck, but because of the fear engendered by the aching. Therefore the diagnosis must be made in a positive manner, and a thorough explanation of the mechanism of the pain must be offered to the patient. Often when the fear of serious disease is removed, the discomfort can be tolerated, although sometimes simple analgesics are needed for control of the pain. When the neck pain is but one manifestation of a severe underlying neurosis, intensive psychotherapy is required.

Drug therapy. In general, the medications used in the treatment of vascular neck pain are the same as those used for the control of vascular headache. These are administered to relieve pain, to prevent attacks, and they comprise four main groups: (1) ergotamine tartrate in its various forms; (2) analgesics; (3) sedatives; and (4) drugs that affect mood, such as the tranquilizers and amphetamines. The pharmacologic treatment is divided into two phases: relief of pain, and prevention of subsequent attacks.

To relieve pain, the simplest effective analgesic should be used. Sometimes aspirin is sufficient. Usually, mixtures of aspirin, phenacetin, and caffeine are efficacious. These mixtures with the addition of codeine give even greater analgesic effect. Darvon,* 32 mg., added to an aspirin-phenacetin-caffeine mixture works satisfactorily in many cases. Ergotamine tartrate is best administered orally in the form of Cafergot† or Cafergot P-B tablets. Since vascular neck pain does not occur in short, severe attacks, the Cafergot dosage is somewhat different from that used in the treatment of vascular headache. Four tablets per day may be given for several days, if necessary. It is best to use an analgesic tablet in conjunction with the ergotamine tartrate. Since there is little nausea and no vomiting associated with vascular neck pain, the parenteral use of ergotamine tartrate is unnecessary.

To prevent attacks, if the periods of neck pain have been frequent or if the aching has persisted for a long time, once the pain has been brought under control, a prophylactic program may be initiated. Often, 4 Bellergal‡ tablets per day, for from four to six weeks, will prevent recurrence. To simplify the administration of Bellergal, the long-acting tablets (Spacetabs) can be used: 1 tablet is taken on arising and 1 tablet again at bedtime. Four Benadryl§ capsules (each capsule 50

** Darvon (dextro propoxyphene hydrochloride), Eli Lilly and Company.*

† Cafergot, Sandoz Pharmaceuticals.

‡ Bellergal, Sandoz Pharmaceuticals.

§ Benadryl hydrochloride (diphenhydramine hydrochloride), Parke, Davis & Company.

mg.) per day may be used for this purpose. Benadryl seems to be more beneficial than are the other antihistaminics, probably because of its sedative or tranquilizing action. In some instances, one of the tranquilizing agents may be administered for several weeks or months to prevent further attacks.

No surgical treatment. Surgical treatment is not recommended. Unnecessary elective procedures, such as thyroidectomy, tonsillectomy, and tooth extraction, should be avoided.

Physical therapy. Prolonged vascular neck pain produces reflex muscle tension that results in soreness of the sternocleidomastoid or posterior nuchal muscles. The application of heat and the use of massage may relieve the secondary muscular soreness in some cases.

Total treatment. A combination of the psychologic and the pharmacologic treatment is most commonly used. A detailed explanation of the origin of the pain and what is known about the mechanism of vascular pain is presented in a simplified form to the patient. The presence of a hypothetic chemical substance that is responsible for overdistention and relaxation of the carotid artery is postulated, and the possible effects of nervous tension and emotion in the production of this hypothetic vasodilating substance is pointed out. The patient is at least reassured that the pain is not imaginary and that something is known of the cause. The patient nearly always fears the presence of cancer, and sufficient time must be taken to give strong reassurance and to explain why the condition could not be due to a malignant tumor.

A prophylactic medical program is outlined. This has many variations, but one of the most satisfactory combinations has been the administration of one Bellergal Spacetab each morning and at bedtime, along with three Compazine* (prochlorperazine) tablets (10 mg., each tablet) per day. For the pain itself, one of the simple analgesic mixtures is prescribed. If codeine is deemed necessary, the patient should be reassured that a few analgesic one-half-grain codeine tablets will not cause addiction. The patient is advised to take the medication for six weeks and then to return for examination if relief is not obtained. Morphine or meperidine hydrochloride never should be used to control vascular neck pain.

Results

After a follow-up period of at least one year, the results of therapy may be grouped in the following four categories relative to the original vascular neck pain: (1) the pain is much less severe or entirely absent; (2) the pain is about the same, but the patient no longer worries about it and is able to tolerate it; (3) the pain is unchanged; the patient complains bitterly; he either has not accepted or has not understood the explanation, and he has seen several other doctors in his search of another diagnosis; and (4) the neck pain has been supplanted by vascular headache. Fortunately, the results in most of the patients who have been seen at least one year after the initial examination, fall into categories 1 and 2.

**Compazine, Smith Kline & French Laboratories.*

Report of Illustrative Cases

Case 1. A 41-year-old housewife was examined here because of sore throat. Ten years previously she was examined here and the diagnosis was chronic nervous exhaustion. The patient stated at the time of the second examination that all her life she had been having periodic sick headaches accompanied by some soreness in the neck. However, during the past year she had frequent bouts of sore throat and no headache, each episode lasting for a few days or a few weeks. The pain was located chiefly in the left side of the neck and was aggravated by bending, jarring, and nervous tension. At the time of the first attack of sore throat, she was treated by her family physician for a cold, and was given a course of penicillin. She was next told she had a goiter and was referred to a surgeon, who found no enlargement of the thyroid gland, and who diagnosed the condition as chronic tonsillitis. A consulting otolaryngologist disagreed with the diagnosis of tonsillitis and treated her for allergy.

General physical examination here revealed normal findings except for the presence of a tender carotid artery on the left side; the thyroid gland was not enlarged; the tonsils were small and not inflamed, and there was no evidence of organic disease of the ears, the nose, the throat, or the sinuses. Laboratory findings were normal. The diagnosis was: chronic nervous tension state and vascular neck pain.

Case 2. A 28-year-old man, a crime investigator for the Bureau of Internal Revenue, was examined here because of headache and swollen glands. An intelligent, conscientious, tense, high-strung person, he was working at a job he thoroughly disliked, since he was temperamentally unsuited for the task of investigating and prosecuting tax evaders. He had feelings of guilt about his work.

The history indicated that the patient had been in good health until three years previously, when he began to have swelling and soreness of the "submaxillary glands," usually of one gland at a time, but sometimes of both glands. The pain and soreness would extend into the jaws and the side of the face. Each time this difficulty persisted for about three months; there was one pain-free interval of 14 months. During those three years, the patient was examined by many otolaryngologists and other physicians, and various diagnoses were suggested. Although a diagnosis of anxiety neurosis had been made, no one could explain the mechanism of the pain in the neck and face associated with the "swollen glands." More recently a diagnosis of tic douloureux had been considered, and the patient was treated with injections of alcohol but no relief was obtained.

The attacks of headache lasted for from one day to one week. The onset of the headache had caused great apprehension, and it was obvious that the young man had read published details of subarachnoid hemorrhage due to ruptured cerebral aneurysm.

When examined here, in addition to having the neck and face pain of long standing, the patient also had headache in the right occipital, temporal, and frontal areas, associated with conjunctival injection of recent onset. The patient was disgruntled, apprehensive, and overconcerned. The right carotid artery was tender, dilated, and throbbing; other physical findings were normal, as were the results of all laboratory tests and the roentgenograms. A neurosurgeon and an otolaryngologist found no evidence of organic disease. The diagnosis was chronic anxiety tension state with vascular neck pain, and associated vascular head and facial pain of recent occurrence.

The patient's insight was poor and treatment was unsuccessful. One and one-half years after the examination, the patient stated that further medical reading had enabled

him to arrive at his own diagnosis of "temporal arteritis," and he was seeking a physician who was adept at treating this condition.

Case 3. A 40-year-old housewife was examined here because of aching in the throat which had persisted for one year. Ten years before the onset of pain, shortly after the birth of her only child, she had a nervous breakdown and was confined to a rest home for two months. After she was discharged she still was nervous and rundown. Her mother had been subject to sick headaches. The patient herself had periodic headaches for many years. The soreness in the neck was located in the carotid area, chiefly on the right side, the patient stating that the soreness felt as though the glands were swollen. The pain and tenderness appeared once or twice each week for about one day, accompanied by a feeling of tightness and choking in the throat. A diagnosis of thyroid dysfunction had been made and for three months each day she took orally three 50-mg. capsules of propylthiouracil. General physical findings were essentially normal; the thyroid gland was palpable, but neither enlarged nor tender, although there was a tender, throbbing carotid artery on the right side. An endocrinologist found no hyperthyroidism or subacute thyroiditis; an otolaryngologist ruled out the presence of organic disease of the ears, the nose, and the throat. A diagnosis of chronic anxiety tension state with vascular neck pain was made.

Comment

The syndrome of vascular neck pain is certainly not new, and, like headache, must be as old as civilization itself. Although it may have been recognized by a few physicians, little has been written about it, and the concept of "vascular headache in the neck" has not been widely disseminated. Although the underlying mechanisms of all the painful vasodilating syndromes of the head and neck probably are the same, the clinical patterns are so different that the division into various groups is logical and of practical value. However, despite the compartmentation of this group into migraine, tension vascular headache, histaminic cephalalgia, hypertensive migraine syndrome, vascular facial pain, and now vascular neck pain, some of the clinical variants are difficult to classify. Thus, whereas a headache with the typical features of migraine or of histaminic cephalalgia is easy to label, there are some head pains that have the characteristics both of migraine and of histaminic cephalalgia. The headache appearing in the presence of benign hypertension may be indistinguishable from migraine, it may have the pattern of an occipital throbbing headache occurring early in the morning, or it may take the form of vascular facial pain. This lack of a single specific form should not disconcert the clinician, since a mixed or changing pattern offers additional evidence of the basic interrelationship.

A carefully taken history often will indicate that the clinical pattern has changed during the years. When migraine does not entirely disappear in the older patient, it often continues in a form that is similar to tension vascular headache, or in the form of typical "hypertensive" headache, even though hypertension is not present. The carotid artery is almost always sore and tender during the course of a migraine attack, vascular facial pain, or tension vascular headache. It is only when the neck pain is unaccompanied by head or facial pain that the diagnosis is not suspected.

Summary

One of the most common causes of pain in the neck is related to overdistention, relaxation, and increased pulsation of the carotid artery. The syndrome of vascular neck pain is closely related to the various forms of extracranial vascular headache. Vascular neck pain has been referred to only occasionally, and apparently never has been described in detail in the medical literature. Most physicians have not made this diagnosis, although the condition is not rare.

Analysis of 100 consecutive cases of vascular neck pain has revealed that it is more common in women than in men in a ratio of about 4 to 1; it occurs at any age, but mostly in the fourth and fifth decades; and usually there is a history of previous vascular headache. The only abnormality revealed by physical examination is the presence of a tender, throbbing carotid artery. The condition is frequently misdiagnosed and therefore is not properly treated. The preferred treatment is similar to that for the other painful vasodilating conditions of the head.

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CONSERVATIVE TREATMENT OF CANCER OF THE PROSTATE: SOME CLINICAL OBSERVATIONS

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MANY statistical reviews have reported the results of various methods used in the treatment of cancer of the prostate. This report presents some typical cases as well as general observations of the effectiveness of conservative measures in the treatment of prostatic carcinoma. Conservative therapy is mainly hormonal treatment, but it also includes simple orchiectomy (in 20 per cent of patients) and even an occasional transurethral resection for the relief of obstructive urinary symptoms.

It is generally agreed that only about 10 per cent of patients are suitable candidates for so-called "radical prostatectomy." Thus, the remaining 90 per cent of patients must be treated by conservative measures. Experience also suggests that these measures may give results in the other 10 per cent of patients which compare favorably with those obtained following radical operation.

Diagnosis

Diagnosis is first made from digital rectal palpation of the prostate; the experienced finger is remarkably accurate. A roentgenogram of the pelvis is useful to rule out (or in) prostatic calculi. When necessary, we obtain a histologic diagnosis from tissue obtained by needle biopsy. Biopsy occasionally has not been done, as in cases of typical advanced cancer or in certain instances of radiographically demonstrable metastasis.

Categories of Cancer

In reviewing the records of patients with cancer of the prostate, one is impressed by the fact that this is not a uniform disease. Cases may be roughly separated into three groups: (1) slowly growing cancer that runs a chronic course; (2) rapidly growing cancer, often far advanced when first seen, which swiftly progresses to fatal termination in spite of all treatment; and (3) an intermediate group of hormone-dependent cancers that may be controlled for long periods by appropriate treatment.

The following is a typical example of cases in group 1.

A 57-year-old man was first examined by us in 1951, at which time a general physical examination revealed a questionable nodule in the left lobe of the prostate. His history indicated that this was first observed six years previously but was disregarded. Three years before our examination, in another city, a urologist noted this nodule and recommended that the patient take stilbestrol. The advice was followed for six weeks, but there was no apparent change in the nodule, and medication was discontinued. In view of this history, we advised continued observation without treatment. He returned in

November, 1953, with the prostatic findings essentially unchanged, but there were pressing reasons for definitive histopathologic diagnosis. Accordingly, a needle biopsy was performed and the specimen of tissue was reported as adenocarcinoma, grade 3. The patient was given stilbestrol, 5 mg. each day. He returned for three follow-up examinations in 1954, apparently in excellent health and with good clinical response to estrogens.

In July, 1956, he returned, in excellent health, but he had voluntarily discontinued taking stilbestrol some six months before, because his breasts became sore. There was no detectable change in the prostate, and the results of the roentgen studies were negative, so we consented to observe him closely while omitting the estrogen therapy; he was warned of the risk involved. In February, 1958, he returned in excellent health, reporting that he was vigorously active in a thriving business. Recent word finds him in continued good health, *now 14 years after a nodule was first palpated in the prostate, histologically verified as adenocarcinoma.*

At the other extreme we may summarize a case representing group 2 (rapidly growing, irreversible cancer).

A 67-year-old man was first examined in November, 1952. Palpation revealed a hard, nodular, fixed prostate from which a perirectal mass extended. A specimen obtained by needle biopsy revealed undifferentiated prostatic carcinoma. There was no roentgen evidence of bony metastasis. A bilateral orchiectomy was performed and the patient was given stilbestrol. Six months later he returned because of pain in the hip and the back. A roentgenogram of the spine and the pelvis showed extensive metastatic lesions in all bones. He was given palliative roentgen therapy, but when last examined in July, 1953, *eight months after his first examination,* he was approaching a terminal phase.

These two cases illustrate the extremes in clinical behavior of prostatic cancer. Between these extremes is a large group of cases in which conservative treatment can be successfully employed. There is at present no complete unanimity of opinion as to the most satisfactory conservative measures to be adopted or the order in which they should be employed. For example, is castration immediately necessary once the diagnosis is established, or will intensive estrogen administration be sufficient, or when is castration most beneficial?

It has been shown, and we have observed in some of our patients with carcinoma of the prostate, that stilbestrol in adequate doses produces a castration effect as measured by the androgen excretion products in the urine. Birke, Franksson, and Plantin[1] studied androgen excretion in patients with carcinoma of the prostate after stilbestrol treatment and orchiectomy. They concluded that the androgen-depressing effects of stilbestrol and of orchiectomy were the same. Stilbestrol, 30 mg. daily for five days, or 10 mg. for two to three weeks, will produce a full castration effect. These studies support our clinical experience and form the rationale for first giving adequate doses of estrogen before advising orchiectomy. This surgical procedure may be held in reserve, as we have seen palliative benefit from orchiectomy in some patients who no longer show favorable response to

stilbestrol. The following case history demonstrates this course of events.

A 62-year-old man was first examined in January, 1957. The diagnosis was cancer of the prostate; it was verified by histologic study of specimens from a needle biopsy. The pathologic report was adenocarcinoma, grade 2. Roentgenograms of the lumbar spine and the pelvis showed evidence of changes suggesting osteoblastic metastasis or Paget's disease. He was immediately given a course of stilbestrol and did well until December, 1958, when he noted increasing pain in the back. An increase in dosage of stilbestrol brought no benefit. In January, 1959, roentgen examination revealed evidence of extensive, mixed, osteolytic and osteoblastic metastasis. Bilateral orchiectomy was performed and the patient experienced remission of the pain.

Metastatic Disease Controlled by Estrogens

The response of metastatic masses to estrogen therapy is often truly dramatic, as in the following case.

A 52-year-old man was referred to Dr. George Crile, Jr., in February, 1956, because of a tumor in the neck. Examination revealed a large mass of lymph nodes filling the entire posterior triangle on the left side of the neck. Study of specimens from a biopsy of a node led to the diagnosis of metastatic carcinoma. Prostatic examination revealed a firm nodule in the left lobe of the prostate. Needle biopsy of the prostate was performed and the report was adenocarcinoma, grade 2. He was given stilbestrol, 10 mg. a day. Three weeks later the mass in the neck had regressed sharply, and in July, 1956, it was "gone." In May, 1958, the referring physician reported the patient to be well with no evidence of recurrence. On November 1, 1959, a phone report indicated that he is well with no recurrence now almost four years after the initial examination. *It should be noted that orchiectomy was not performed in this case.*

We have had patients in whom a large mass extending from the prostate has produced ureteral obstruction. In several the mass was clearly palpable as an abdominal mass.[2]

A 58-year-old man was examined in November, 1954, because of mild obstructive symptoms. Digital examination of the prostate revealed a fixed, hard, nodular gland with a mass extending upward from the right lobe. An intravenous urogram showed evidence of delayed and diminished function on the right side, with grade 3 hydronephrosis noted in the 60-minute film. He was advised to take stilbestrol, 5 mg. per day. Prompt clinical improvement and relief of the obstructive symptoms ensued. Within eight weeks the mass above the prostate receded, and an intravenous urogram repeated nine months later showed evidence of prompt and normal right renal function with complete disappearance of the hydronephrosis. The patient remained well for four years and died suddenly apparently of a heart attack.

Metastatic disease in bone may likewise show marked regression under hormonal management; one of our most outstanding examples follows.

A 49-year-old man when first examined in December, 1942, by Dr. Charles C. Higgins, had a stony hard, nodular prostate; there was evidence on roentgenograms of

metastatic disease in the lumbar spine and the pelvis. In order to relieve obstructive symptoms, a transurethral resection was performed. The pathologic diagnosis of tissue removed was adenocarcinoma, grade 3. Bilateral orchiectomy was performed and the patient was advised to take stilbestrol. When he was examined in January, 1945, the patient was in good health, and a roentgenogram of the lumbosacral spine and the pelvis revealed no evidence of metastasis. He reported in good health for periodic follow-up examinations, and in April, 1958, he returned for removal of a stone in the bladder. Roentgenograms of bone again showed no evidence of metastasis. The patient was examined in November, 1959; he felt well, and the result of the roentgen study was negative, *17 years having elapsed since the original diagnosis of cancer of the prostate with bony metastasis.*

Certain unusual types of cases deserve special mention.

A 50-year-old man was first examined in the Department of Dermatology by Dr. George H. Curtis, in February, 1956, because of a skin eruption on the face, and great generalized weakness to the point of inability to move the arms. A diagnosis of dermatomyositis was made. Physical examination revealed an enlarged supraclavicular lymph node, which was removed for biopsy. It was diagnosed as metastatic adenocarcinoma. At first examination the prostate had excited no suspicion, but re-examination revealed suggestive nodularity with fixation. A specimen removed by needle biopsy was diagnosed as adenocarcinoma with perineural lymphatic invasion. The patient was treated with intravenous estrogens, and later stilbestrol. There was prompt improvement with clearing of the skin eruption and the return of normal full use of his arms. The patient was still well at the time of the last follow-up report in January, 1959.

Dr. Arthur L. Scherbel, in the Department of Rheumatic Disease, has under observation five patients who were examined because of pain diagnosed as typical of rheumatoid arthritis. Each patient had carcinoma of the prostate, as verified by histologic study of tissue removed at needle biopsy. After administration of stilbestrol, and no other hormone, all had prompt and complete remission of their arthritic symptoms and have remained well for from one to four years. In none of these patients was there roentgen evidence of bony metastasis.

Discussion

The above-mentioned isolated case reports, of interest in themselves, assume more significance when we realize that they are illustrative of larger groups of patients. The cumulative effect of observing the favorable response to hormonal therapy in some of the advanced cases of prostatic cancer raises the question: If this is so good for the advanced cases, why is it not equally good or better for the so-called "early" cases? There is some difficulty in knowing when a case is truly early in a surgical sense. Franks,[3,4] in studying the spread of prostatic cancer, found invasion of the capsule in 75.4 per cent of 69 cases of unsuspected cancer. Invasion of lymphatic and blood vessels was common, and perineural infiltration was found in 31.9 per cent of cases.

There is divided opinion as to when estrogen therapy should be started even in proven carcinoma of the prostate. We have chosen to start therapy when the

diagnosis is made, though some physicians believe that it should be reserved until troublesome symptoms develop. Neither is there general agreement as to when orchiectomy should be performed. Since administration of estrogens has been shown to produce a castration effect, there appears to be no need to include orchiectomy as a part of the original plan of treatment. We have performed orchiectomy in only 20 per cent of patients, and many of these have followed full courses of stilbestrol administration.

Mention should be made of the use of cortisone in conservative treatment. We have used cortisone in a small group of patients who have deteriorated after administration of estrogens or after castration, or after both types of therapy. Transient improvement may be noted and the use of cortisone is recommended, although dramatic and long-term improvement cannot be expected.

Conclusion

It is estimated that from 80 to 85 per cent of prostatic cancers are hormone-dependent, and that benefit from conservative or hormonal treatment may be expected. There is no reliable and simple method for determining which tumors are sensitive, or their degree of sensitivity. At present, this can be determined only by empirically using estrogens on each patient.

The benefits of hormonal treatment of cancer of the prostate are more keenly appreciated if one's experience goes back to pre-stilbestrol days. Today it is uncommon to see the painful and prolonged terminal illness commonly seen in past years. With increasing frequency our records show that patients with prostatic carcinoma who are on hormonal treatment, die of other diseases. It has been said that there is no case on record of a permanent cure with hormonal therapy, yet there are many cases in which normal life expectancy has been given to the patient, and death was not related to his prostatic disease.

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RECURRENT LYMPHANGITIS OF THE LEG ASSOCIATED WITH DERMATOPHYTOSIS

Report of 25 Consecutive Cases

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THE syndrome of recurrent lymphangitis, often resulting in permanent lymphedema, has been recognized for many years. Ochsner, Longacre, and Murray[1] gave a comprehensive discussion of this syndrome in 1940, and yet, even today, the clinical diagnosis of acute lymphangitis is frequently missed. Moreover, the cause of the recurrent attacks of lymphangitis is still not clear. Some authors[2,3] believe that recurrence is secondary to foci of infection in the body. Others[4] believe that recurrence is due to an acquired hypersensitivity of previously infected tissues. The majority of authors believe that usually there is some portal of entry for bacteria through the skin in order to cause the lymphangitis.

That there is more than a casual relationship between dermatophytosis (athlete's foot) and the repeated attacks of lymphangitis has been suggested by Allen and Ghormley,[5] by Sulzberger, Rostenberg, and Goetze,[6] and in several textbooks.[7-11] It is the purpose of this paper to discuss 25 consecutive cases of recurrent lymphangitis associated with dermatophytosis treated at the Cleveland Clinic in the years 1950 through 1958, and the clinical course subsequent to treatment.

Clinical Signs and Symptoms

The attacks of lymphangitis are characteristic in the acuteness of their onset and the severity of the systemic reaction. They usually occur suddenly, without warning, and within a few hours the symptoms are extremely severe. Occasionally there is a dull pain in the affected extremity, which rapidly becomes acute. A severe, shaking chill with fever as high as 106 F. usually initiates the attack. Associated symptoms include malaise, anorexia, headache, nausea and vomiting. The regional lymph nodes of the extremity often become swollen and tender. On the affected limb a small red area may appear, which rapidly spreads so that soon a considerable part of the extremity is red, swollen, and tender. Frequently there are red streaks running along the course of the lymphatic vessel. A fever persists from a few hours to two or three days. The chills may recur every few hours. The duration of the attacks varies from 2 to 14 days, but there is a characteristic, quick response to penicillin or to penicillin-like drugs. Some residual swelling may persist after all the clinical signs of acute inflammation have disappeared.

The intervals between attacks vary greatly. They may occur as frequently as once a week, but usually they are several months apart. As the disease advances and the lymphedema worsens, the periods between attacks usually become shorter.

Single attacks of lymphangitis do not as a rule result in persistent lymphedema. However, with each subsequent attack the edema becomes more severe and even-

tually becomes irreversible. Thus it is important not to ignore the early attack, but to treat it and its source quickly.

Cases of acute lymphangitis with cellulitis are most frequently misdiagnosed as thrombophlebitis, though the differential diagnosis is usually quite easy to make. The distinguishing characteristics are summarized in *Table 1.*

Table 1.—*Differential diagnosis of inflammation of the leg: lymphangitis with cellulitis, superficial thrombophlebitis, and iliofemoral thrombophlebitis*

Differential features	Lymphangitis with cellulitis	Superficial thrombophlebitis	Iliofemoral thrombophlebitis
Onset	Sudden	Gradual	Gradual
Fever	High—up to 106 F.	Mild—99 to 101 F.	Rarely more than 102 F.
Chills	Common	Rare	Rare
Lymphadenopathy	Common	Rare	Rare
Portal of entry for infection	Usual	Rare	Rare
Palpable, inflamed vein	Rare	Usual	Common
Red streaking of skin	Common	Common	None
Size of limb	Enlarged	Normal	Enlarged
Superficial veins	Normal	Normal	Distended
Skin temperature of limb	High	High	Usually normal
Response to penicillin	Rapid	None	None

Clinical Data

Twenty-five cases of recurrent lymphangitis associated with dermatophytosis have been treated at the Cleveland Clinic in the years 1950 through 1958 *(Table 2).* There are from one to eight year follow-up records on 20 patients. One patient died, and four patients were lost to follow-up. The age range was 22 years to 67 years. There were 9 women and 16 men; they had from 2 to 32 attacks of lymphangitis in from 1 to 30 years. The most unfortunate patient had 30 attacks within three years.

Of 16 patients who had been given diagnoses before being examined here, 13 patients were told that they had either thrombophlebitis or recurrent thrombophlebitis. Three patients were thought to have cellulitis. A diagnosis of rheumatic fever was considered in two patients, osteomyelitis in one patient.

One patient (no. 13, *Table 2*) apparently had a flare-up of nephritis with gross

Table 2.—*Data on 25 consecutive patients who had recurrent lymphangitis of the leg with dermatophytosis treated at Cleveland Clinic (1950 through 1958)*

Case no.	Age, years	Sex	Attacks, total number	Interval since first attack, years	Attacks since treatment, number	Follow-up, years	Recurrent fungus since treatment
1	55	F	3	1	1	5	Yes
2	46	M	30	3	1	4	Yes
3	41	M	15	1	5	4	Yes
4	44	F	4	10	1	5	Yes
5	22	M	24	12	7	7	Yes
6	59	M	6	30	0	4	No
7	38	F	3	3	0	4	No
8	63	M	14	4	0	3½	No
9	33	M	2	1	0	7	No
10	34	M	16	7	0	4	No
11	31	M	13	2	0	1¾	No
12	37	F	26	10	0	2½	No
13	33	F	"Many"	15	0	4	No
14	57	M	5	5	0	7	No
15	31	M	7	9	0	6	No
16	53	M	4	8	0	8	No
17	67	M	5	5	0	5	No
18	37	F	11	2	0	1	No
19	30	M	2	1	0	1	No
20	55	F	20	2	0	6	No
21	63	F	4	6	Deceased		
22	29	M	2	1	Lost to follow-up		
23	33	F	5	20			
24	30	M	"Several"	17			
25	22	M	"Several"	2			

hematuria during each attack of lymphangitis, an association that strengthened the belief that the lymphangitis was of streptococcal origin.

All patients had dermatophytosis proved by potassium hydroxide preparations

of skin scrapings. All were treated with undecylenic acid-zinc undecylenate ointment, sometimes in combination with Whitfield's ointment, in the manner outlined under *Prevention of future attacks.*

Mild to moderate lymphedema was noted in 12 patients when first examined, and two had severe lymphedema. In the follow-up questionnaires, 10 patients reported some swelling of the legs and feet, which disappeared at night. Only three patients stated that they had swelling that persisted day and night.

A striking fact is that, of the 20 patients who were followed, 15 have had no further attacks. These patients stated that they have been able to keep their feet free of dermatophytosis. Of the five patients who have continued to have attacks, all still have dermatophytosis.

Treatment

Treatment of the acute attack. Acute attacks of lymphangitis will usually subside spontaneously within 4 to 14 days; however, the response to penicillin and similar antibiotics is usually quite dramatic within one to three days. Additional measures to be taken include bed rest, elevation of the affected extremity, and the application of warm, moist packs.

Prevention of future attacks. In addition to the specific therapy in acute lymphangitis, between attacks it is important that edema of the limb be controlled as much as possible because the edematous tissue is highly susceptible to infection. A properly fitted elastic stocking to control the swelling in the leg should be worn at all times when the patient is up and about. The affected leg should be elevated at night and whenever possible during the day. An occasional course of oral diuretics may be needed. With more resistant edema, pneumatic massage and precise fitting with a prestressed, elastic sheath as outlined by Brush and associates,[12] and by Britton[13] may be necessary. This control of edema can be a major factor in preventing future attacks.

The sources of infection and reinfection must be eradicated. This is especially necessary when there is dermatophytosis. An ointment containing undecylenic acid and zinc undecylenate is usually prescribed to be applied between the toes twice daily until all obvious infection has cleared, usually for about two weeks. After the skin has healed, the ointment is applied once each week, and a powder containing the same ingredients is dusted in the shoes and the stockings about three times weekly. Patients are advised to dry well between the toes after bathing and to wear clean stockings daily. This treatment should be followed indefinitely. For the more resistant cases, especially those in which there is onychomycosis, the new oral antifungal preparation griseofulvin is proving especially effective.

Discussion

The patient who has repeated attacks of a red-hot, painful, swelling of the leg can present quite a problem in diagnosis to the physician who is unaware of the clinical entity of recurrent lymphangitis. Idiopathic recurrent thrombophlebitis

may be strongly suspected, and a fruitless, expensive search may be made for occult carcinoma. A needless, potentially dangerous course of prophylactic anticoagulants may be tried. A frustrating situation occurs when the patient continues to have repeated attacks despite the application of the best diagnostic and therapeutic measures known to the physician.

It has long been recognized that there is usually some break in the skin to serve as a portal of entry for bacteria in cases of lymphangitis. A break such as a wound, cut, ulcer, abrasion, contusion, scratch, hangnail, pinprick, or vesicle, usually can be found if a careful search is made. Even minor abrasions with the slightest wound of the corium may tear open lymph vessels and permit direct entry of bacteria. Dermatophytosis with moist, warm, macerated skin, and fissures between the toes provides an ideal medium and entry for bacteria. Also, because of its chronic nature, it provides a portal of entry for repeated attacks of the bacteria on the lymphatic system over periods of months and years.

When bacteria enter the lymphatic vessels a spreading, obliterative lymphangitis develops. Attempts to find the causal organism are usually unsuccessful. It is said that in 1892 Sabouraud first demonstrated the presence of the streptococcus organism in patients with recurrent lymphangitis.[1] In 1930, Suarez[14] reported a study of 60 cases of recurrent lymphangitis, and cultures obtained from the specimens of subcutaneous tissue in 50 patients were negative in all but two patients; streptococci were found in both of them. The streptococcus often can be isolated from fissures of the skin associated with dermatophytosis.

The lymphangitis causes thrombosis and thereby occlusion of the lymph vessels. The inflammatory reaction causes excess accumulation of proteins in the interstitial fluid. This storing up of proteins sets up a vicious cycle, for the flow of lymph is impeded and still more proteins accumulate. The protein and other products of inflammation are ideal for the growth of fibroblasts and the production of scar tissue. Drinker, Field, Ward, and Lyons[15] demonstrated that the lymphedema fluid itself is a rich medium for bacteria, and greatly increases the chances for future attacks of lymphangitis. With each subsequent attack the affected area becomes larger and there is thickening and scarring of the subcutaneous tissue; eventually typical elephantiasis with massive limbs may result. It is important to recognize this clinical entity of recurrent lymphangitis in its early stages before much permanent damage has been done.

Summary

Recurrent lymphangitis is a well-defined but too frequently misdiagnosed clinical entity. It is characterized by sudden, repeated attacks of a red-hot, painful, swelling of the leg. Proper diagnosis is essential. Treatment includes bed rest, elevation of the leg, elastic-sheath covering of the leg if needed. When dermatophytosis is also present, appropriate local therapy and, if indicated, griseofulvin are used. This therapy must be instituted early in the course of the disease to preclude massive edema and elephantiasis.

The data of 25 consecutive cases of recurrent lymphangitis associated with dermatophytosis have been presented; the clinical course after treatment is included. After the dermatophytosis cleared and the edema was controlled, no future attacks occurred in 15 patients. Recurrent attacks of lymphangitis continued in five patients who were unable or were unwilling to control the dermatophytosis.

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HEADACHE—A COMMON SYMPTOM IN THROMBOSIS OF THE INTERNAL CAROTID ARTERY

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INCREASING employment of anticoagulant therapy and direct surgical operation in the treatment of thrombosis of the internal carotid artery has stimulated interest in the clinical recognition of the condition. Visual disturbances (field defects, blurring of vision, scotomata and amblyopia of the eye on the affected side), aphasia, hemiparesis or monoplegia, sensory disturbances of the anus or legs, psychiatric symptoms, convulsions (often the jacksonian type) and headaches are the common manifestations.[1-7] Three clinical types of onset occur: in one group the onset is sudden and the symptoms are severe (usually hemiparesis); episodic symptoms occur in a second group, symptoms often being absent between attacks; in a third group the symptoms are slowly progressive, resembling the manifestations of an intracranial neoplasm.

Our records of 56 cases of thrombosis involving the internal carotid arteries have been reviewed. All diagnoses were confirmed by arteriograms, and operative proof was secured in all 24 of the patients who underwent surgical procedures. In 35 patients, episodic symptoms occurred; in 14 patients the symptoms were sudden and severe; and in 7 patients the symptoms were slowly progressive. *Table 1* shows the initial symptoms, the incidence of single symptoms, and the frequencies of various symptoms. Multiple symptoms occurred in most patients; some patients had several symptoms simultaneously at the onset of the disease; headache was the commonest initial single symptom. These observations correspond with those reported by others.

Headache occurred in 28 patients, being an initial symptom in 13 patients, in 11 of whom it was the single initial symptom. Headache was almost always unilateral, and always occurred on the side of the arterial involvement. There were no prolonged severe headaches and in no case did the headache antedate neurologic manifestations by a prolonged interval.

Headache was a common manifestation in the 14 patients who had sudden and severe symptoms and in the 35 patients who had episodic symptoms, but it was not manifested in the 7 patients who had the slowly progressive symptoms. The slowly progressive symptoms of thrombosis of the internal carotid artery are most likely to be confused with those of intracranial aneurysm.

In 32 patients, the protein content of the spinal fluid was determined; in 12 patients it exceeded 45 mg. per 100 ml. The protein content ranged between 46 mg. and 120 mg.; being 50 mg. or more in 11 patients, more than 65 mg. in 5 patients, and more than 100 mg. in 2 patients. In each of the patients having a high protein content in the spinal fluid, headache was a symptom. In contrast, headache occurred in only 9 of 19 patients having normal protein content in the

Table 1.—*Symptoms in 56 patients who had thrombosis of the internal carotid artery*

Symptoms	Total frequency, no. of patients	Initial symptom, no. of patients	Single initial symptom, no. of patients
Hemiparesis	41	14	7
Monoplegia	23	11	6
Arm	(19)	(8)	(3)
Leg	(4)	(3)	(3)
Sensory effects			
Arm	28	11	5
Leg	14	2	2
Aphasia	40	12	4
Visual disturbances	35	6	4
Headache	28	13	11
Mental disturbances	16	—	—
Convulsions	13	—	—

spinal fluid (one of the 32 patients was excluded because there was blood in a tap specimen). There is no obvious explanation for the apparent association of an increase in protein in the cerebrospinal fluid with headache. There seemed to be no association between the severity of clinical manifestations and the occurrence of headache or the occurrence of high protein content in the cerebrospinal fluid.

Summary

Unilateral headache on the side of arterial involvement is a common manifestation of thrombosis of the internal carotid artery of the sudden or of the episodic type of clinical onset. Headache occurred in half of a series of 56 patients who had thrombosis of the internal carotid artery; it was not present in seven patients of the series who had slowly progressive symptoms. Headache was a symptom in every patient who had a high protein content in the cerebrospinal fluid, an apparent association that is not readily understood.

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THYROID FUNCTION MEASURED BY IN VITRO ERYTHROCYTE UPTAKE (RED-CELL UPTAKE) OF I^{131}-LABELED *l*-TRIIODOTHYRONINE*

Results of 133 Determinations

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SINCE it is now known[1-3] that there are differences in the amount of thyroxin-binding protein in the blood, in the various grades of thyroid activity, the work of Hamolsky and associates,[4,5] and Crispell, Kahana, and Hyer[6] suggested that one might estimate the amount of thyroxin-binding protein, and study thyroid function clinically, by the in vitro erythrocyte uptake of I^{131}-labeled *l*-3, 5, 3 prime-triiodothyronine (TRI^{131} red-cell uptake, hereinafter called RCU). Others have shown that there are many factors that altered the RCU of *l*-triiodothyronine other than the grade of thyroid function. It is decreased in pregnancy,[4-8] during estrogen therapy, and increased with Dicumarol† therapy, nephrosis, hepatic disease, emphysema, and severe illness[9] of any cause. Since the evidence to date indicates that this parameter of thyroid function is rarely affected by exogenous iodine medication, there are many[4-8] who believe it probably will have considerable clinical usefulness. This report is a summary of our experience with 133 determinations in patients who had various thyroid disorders.

Method

As previously described by Hamolsky and associates,[4,5] and by Crispell, Kahana, and Hyer[6] the method consists principally of adding a standard solution of TRI^{131} to 5 ml. of oxalated, citrated, or heparinized blood. In our initial experiment, oxalated blood was used, but now EDTA‡ is used as an anticoagulant. The blood was collected in a commercially prepared vacuum collection tube, and it was found that some coagulation took place when the TRI^{131} was added to the oxalated blood unless the amount of oxalate in the tube was doubled, and unless oxalate was added to the saline solution used for washing the cells. EDTA prevented this coagulation and in addition decreased the hemolysis during the washing procedure.

The TRI^{131} solution was added to the specimen in the collecting tube so that

**The radioactive material (Radio-L-Triiodothyronine Sterile Solution) used in this investigation was supplied by Abbott Laboratories on the authorization of the Isotopes Division, United States Atomic Energy Commission, Oak Ridge, Tennessee.*

†Dicumarol, Abbott Laboratories.

‡EDTA is dipotassium-ethylenediaminetetraacetate.

when 1 ml. of the TRI^{131}-blood mixture was tested in a scintillation (well) counter,* about 8,000 to 10,000 counts per minute were registered. This was determined by experience to be the optimum amount of radioactive material to give the most consistent and reproducible results. After adding the TRI^{131}, the blood was incubated on a vertically rotating mixing wheel at 37 C. for three hours. At the end of the incubation time, three aliquots of 1 ml. each were taken for analysis. The first aliquot was used as the whole blood control, and was pipetted directly into a 12 mm. by 100 mm. test tube and held until the other aliquots had been processed. The other two aliquots were duplicate specimens used to measure the residual radioactivity present after washing the cells four times with physiologic saline solution. These specimens were pipetted directly into polystyrene, round-bottom centrifuge tubes, 15 mm. by 100 mm. This plastic is believed to cause less hemolysis than does glass; the tube can be freed from radioactivity faster than can glass after it has been used, and, moreover, plastic eliminates breakage. After the cells were washed, they were lysed and were transferred quantitatively to the test tubes. The three tubes were then made up to equal volumes with distilled water, which also lysed the cells. Radioactivity of the material in the tubes was determined with a scintillation (well) counter. Three one-minute counts were taken for each specimen. The RCU was calculated by dividing the counts of the washed cells by the counts of the whole blood, multiplying the result by 100, and correcting for cell volume. The results were then reported as per cent per 100 per cent hematocrit reading. The formula is:

$$\text{RCU} = \frac{\text{Counts of washed cells}}{\text{Counts of control tube}} \times \frac{100}{\text{Hematocrit reading, ml./100 ml.}}$$

One hundred thirty-three determinations were done on hospital or clinic patients who also underwent the standard tests for thyroid function; these included: protein-bound iodine, basal metabolic rate, and radioiodine uptake. The final diagnosis was then compared with results of the RCU.

Results *(Fig. 1)*

Euthyroidism. Seventy-nine euthyroid patients were studied in the manner described, and the results were tabulated. The range of the RCU was from 12 per cent to 26.5 per cent, or an average of 17.8 per cent. Seventy-one patients (90 per cent) had values over 14 per cent; 74 patients (94 per cent) had values under 22.5 per cent; and 77 patients (97 per cent) had values under 24.0 per cent. It should be noted that 97 per cent of patients (77) had values between 12.0 and 24.0 per cent; whereas, 81 per cent of patients (64) had values between 14.0 and 22.5 per cent.

Hyperthyroidism. The 40 patients with active hyperthyroidism (Graves' disease) had an average RCU of 29.5 per cent in a range of 10.8 to 89.1 per cent. Twenty-six

**The determinations were made with the technical assistance of Miss Doris Reep, under the guidance and with the co-operation of Dr. Otto Glasser and Mr. Bernard Tautkins, Department of Biophysics.*

THYROID FUNCTION MEASURED BY IN VITRO ERYTHROCYTE UPTAKE (RED-CELL UPTAKE) OF I^{131}-LABELED *l*-TRIIODOTHYRONINE*

Results of 133 Determinations

O. PETER SCHUMACHER, M.D., Ph.D.,
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SINCE it is now known[1-3] that there are differences in the amount of thyroxin-binding protein in the blood, in the various grades of thyroid activity, the work of Hamolsky and associates,[4,5] and Crispell, Kahana, and Hyer[6] suggested that one might estimate the amount of thyroxin-binding protein, and study thyroid function clinically, by the in vitro erythrocyte uptake of I^{131}-labeled *l*-3, 5, 3 prime-triiodothyronine (TRI^{131} red-cell uptake, hereinafter called RCU). Others have shown that there are many factors that altered the RCU of *l*-triiodothyronine other than the grade of thyroid function. It is decreased in pregnancy,[4-8] during estrogen therapy, and increased with Dicumarol† therapy, nephrosis, hepatic disease, emphysema, and severe illness[9] of any cause. Since the evidence to date indicates that this parameter of thyroid function is rarely affected by exogenous iodine medication, there are many[4-8] who believe it probably will have considerable clinical usefulness. This report is a summary of our experience with 133 determinations in patients who had various thyroid disorders.

Method

As previously described by Hamolsky and associates,[4,5] and by Crispell, Kahana, and Hyer[6] the method consists principally of adding a standard solution of TRI^{131} to 5 ml. of oxalated, citrated, or heparinized blood. In our initial experiment, oxalated blood was used, but now EDTA‡ is used as an anticoagulant. The blood was collected in a commercially prepared vacuum collection tube, and it was found that some coagulation took place when the TRI^{131} was added to the oxalated blood unless the amount of oxalate in the tube was doubled, and unless oxalate was added to the saline solution used for washing the cells. EDTA prevented this coagulation and in addition decreased the hemolysis during the washing procedure.

The TRI^{131} solution was added to the specimen in the collecting tube so that

**The radioactive material (Radio-L-Triiodothyronine Sterile Solution) used in this investigation was supplied by Abbott Laboratories on the authorization of the Isotopes Division, United States Atomic Energy Commission, Oak Ridge, Tennessee.*

† Dicumarol, Abbott Laboratories.

‡EDTA is dipotassium-ethylenediaminetetraacetate.

when 1 ml. of the TRI^{131}-blood mixture was tested in a scintillation (well) counter,* about 8,000 to 10,000 counts per minute were registered. This was determined by experience to be the optimum amount of radioactive material to give the most consistent and reproducible results. After adding the TRI^{131}, the blood was incubated on a vertically rotating mixing wheel at 37 C. for three hours. At the end of the incubation time, three aliquots of 1 ml. each were taken for analysis. The first aliquot was used as the whole blood control, and was pipetted directly into a 12 mm. by 100 mm. test tube and held until the other aliquots had been processed. The other two aliquots were duplicate specimens used to measure the residual radioactivity present after washing the cells four times with physiologic saline solution. These specimens were pipetted directly into polystyrene, round-bottom centrifuge tubes, 15 mm. by 100 mm. This plastic is believed to cause less hemolysis than does glass; the tube can be freed from radioactivity faster than can glass after it has been used, and, moreover, plastic eliminates breakage. After the cells were washed, they were lysed and were transferred quantitatively to the test tubes. The three tubes were then made up to equal volumes with distilled water, which also lysed the cells. Radioactivity of the material in the tubes was determined with a scintillation (well) counter. Three one-minute counts were taken for each specimen. The RCU was calculated by dividing the counts of the washed cells by the counts of the whole blood, multiplying the result by 100, and correcting for cell volume. The results were then reported as per cent per 100 per cent hematocrit reading. The formula is:

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(65 per cent) hyperthyroid patients had values above 26.5 per cent, which was the highest value obtained in euthyroid patients. Thirty-six (90 per cent) hyperthyroid patients had values higher than 22.5 per cent *(Table 1)*, and 38 patients (95 per cent) had values higher than 21.0 per cent.

Hypothyroidism. The 14 patients with myxedema had an average RCU of 11.1 per cent. All of these patients had values below 14.5 per cent; 12 patients (86 per cent) had values below 14.0 per cent *(Table 1)*; and 9 (65 per cent) had values under 12.0 per cent.

Continuing Studies on the Same Patients

Table 2 lists the RCU values for eight hyperthyroid patients before and during therapy. There is good correlation between the patient's clinical response and the

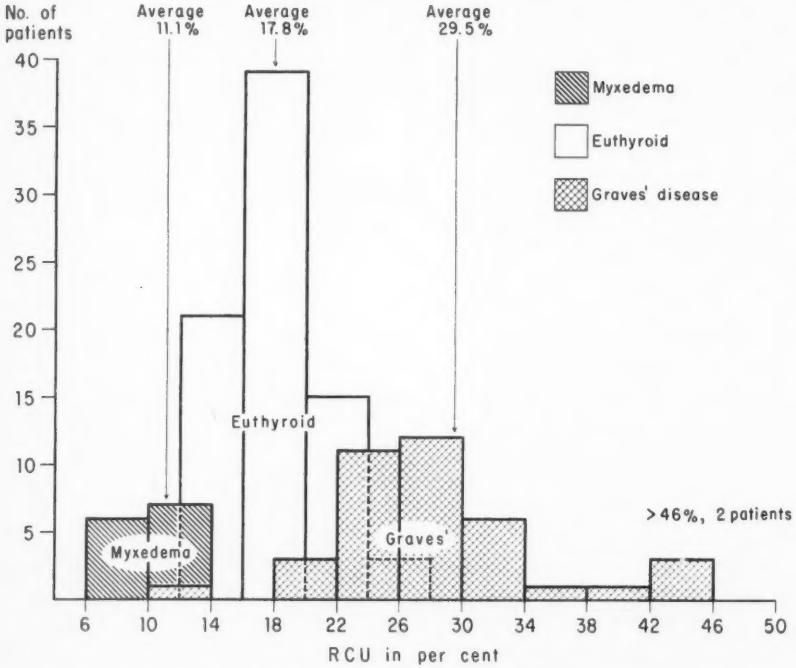

Fig. 1. Graph showing the results of the RCU in 14 patients with myxedema, 79 euthyroid patients, and 40 hyperthyroid patients. The number of patients with values of the RCU in intervals of 4 per cent is plotted vertically. There were no patients with myxedema with values above 14 per cent (actual range 6.5 to 14.5 per cent). The euthyroid patients had values between 12 and 28 per cent (actual range 12 to 26.5 per cent). The hyperthyroid patients had values between 10 and 86 per cent (actual range 10.8 to 89.1 per cent).

change in the RCU. The usefulness of the radioiodine tracer in diagnosing thyroid overactivity becomes impaired[10] after radioiodine therapy or after surgery. Perhaps the RCU will be particularly useful in treated patients.

Table 1.—*Summary of 133 determinations of RCU*

	Thyroid status	
	Myxedema	Euthyroid
Average RCU	11.1% *Under 14.0% (86%)*	17.8% *Over 14.0% (90%)*
	Hyperthyroid	
Average RCU	29.5% *Over 22.5% (90%)*	17.8% *Under 22.5% (94%)*

Table 2.—*Comparison of the RCU in eight hyperthyroid patients before and during treatment*

	% RCU, phase			
Patient no.	Toxic	Incomplete treatment	Euthyroid	Myxedema
1	61.7	23.5	12.5	—
2	21.1	—	14.3	—
3	43.9	28.0 (Lugol's solution)	—	—
4	30.2	—	15.6	—
5	32.0	—	16.0	—
6	26.3	—	20.0	12.9
7	22.7	—	—	7.7
8	—	—	17.24	10.8

Factors That Affect the RCU

Since we have not had the opportunity to make a systematic study of the factors that alter the RCU, we are unable to draw any conclusions in this regard, although we have studied seven pregnant, healthy patients who had low normal values, as has been previously[5] described, and have observed unusually high values

in an occasional patient taking Dicumarol. Other cases in which there may have been factors influencing the RCU are summarized in *Table 3.*

Table 3.—*Alterations in the RCU in eight patients*

Patient no.	Summary of data
1	Myxedema; PBI, 8.3 μg./100 ml.; B.M.R. (−29%); RCU, 16.4%; gallbladder roentgenograms 2 months before studies.
2	Active Graves' disease; PBI, 8.1 μg./100 ml.; B.M.R. (+20%); RCU, 21.1%; Lugol's solution until 1 week before studies.
3	Emphysema; euthyroid; RCU, 34.9%.
4	Euthyroid; bromism (serum bromide, 170 mg./100 ml.); RCU, 27.6%.
5	Myxedema with postnecrotic cirrhosis; RCU, 19.6%.
6	Euthyroid with severe intercapillary glomerulosclerosis; RCU, 26%.
7	Severe Graves' disease with severe secondary hepatic disease; Bromosulphalein, 28%; RCU, 6.0% with active hyperthyroidism; RCU, 20.3% when euthyroid.
8	Graves' disease; B.M.R. (+20%); PBI, 8.0 μg./100 ml.; RCU, 21.8%; Lugol's solution until 3 weeks before studies.

We have observed *(Table 2)* that there is an excellent correlation between the change in the RCU and the patient's clinical response, particularly in the treatment of hyperthyroidism. Because of its effect on thyroid function, iodine may indirectly influence the RCU. One patient (case 3, *Table 2),* in whom the RCU was greatly changed by Lugol's solution also had an excellent clinical response to 10 days of this therapy. Two patients (cases 2 and 9, *Table 3)* also had RCU values considerably lower than the average value obtained in hyperthyroidism (29.5 per cent). Both of the patients had had excellent clinical responses to Lugol's solution.

Discussion

As has been previously shown with paper electrophoresis,[1-3] small amounts of I^{131}-labeled thyroxin or *l*-triiodothyronine are localized in the inter-alpha-globulin zone at pH 7.4 and 8.6. Further studies disclosed that in blood from patients with various thyroid disorders, the amounts of added I^{131}-labeled thyroxin or *l*-tri-

iodothyronine bound by the thyroid-binding globulin varied inversely with the thyroid function, indicating that in hyperthyroidism, the thyroid-binding globulin is relatively saturated as compared with the thyroid-binding globulin in hypothyroidism. This saturation can be measured indirectly by the RCU.

Hamolsky, Stein, and Freedberg[4] observed that the red-cell uptake in the euthyroid range was principally between 10.3 and 17.0 per cent. In the series reported by Ureles and Murray[8] the range was between 11.5 and 18.5 per cent. Our values are considerably higher than those (14.0 to 22.5 per cent); the reason for this difference is not obvious, although we used plastic tubes instead of glass flasks for the washing. Ureles and Murray[8] stated that determinations carried out in open flasks were significantly depressed and led to false values, but this was not a factor here, since the tubes were all stoppered. We have not as yet studied enough patients with various conditions that alter the thyroxin-binding protein, to draw any firm conclusions as to what other factors may alter the results of this test.

Summary and Conclusions

Patients with various grades of thyroid function were studied with the in vitro test of erythrocyte or red-cell uptake of I^{131}-labeled *l*-triiodothyronine (RCU). The average value for patients with myxedema was 11.1 per cent, for euthyroid patients was 17.8 per cent, and for hyperthyroid patients with hyperthyroidism due to Graves' disease was 29.5 per cent. Twelve (86 per cent) of 14 patients with myxedema had values under 14.0 per cent. Of 79 euthyroid patients, 71 (90 per cent) had values higher than 14.0 per cent. Of 40 patients with hyperthyroidism secondary to Graves' disease, 36 patients (90 per cent) had values more than 22.5 per cent. In comparison, 74 patients (94 per cent) of the euthyroid group had values less than 22.5 per cent. It is obvious that some values obtained in euthyroid patients overlap some of those obtained in hyperthyroid and hypothyroid patients.

The measure of the clinical usefulness of the RCU, as with all thyroid-function tests, will depend on further understanding of those pathologic states that affect the RCU, and which are not related to the patient's thyroid function. The test has the advantage that no radioactive substance is administered to the patient, and it is relatively easy to do in comparison with the test for protein-bound iodine. The results are also unaffected by the previous administration of iodine.

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LETTER TO THE EDITOR,
Cleveland Clinic Quarterly:

In regard to my paper entitled "Management of Peripheral Edema, Including Lymphedema of the Arm After Radical Mastectomy," published in the *Cleveland Clinic Quarterly,* Volume 26, No. 2, April, 1959, pages 53 through 61, it may not have been made clear that the treatment was based on the earlier work of others. It is believed that the first work (unpublished) was carried out by Dr. Frederick A. Coller of the University Hospital of Ann Arbor, Michigan, in conjunction with Mr. Conrad Jobst. Dr. William T. Foley[1] reported certain aspects of the treatment of edema of the arm in 1951. It was further developed by Doctors Brush and Heldt,[2] and by Doctors Brush, Beninson, Wylie, Block, and Heldt[3] of the Henry Ford Hospital, Detroit, Michigan, whose reports were published in 1955 and 1958, respectively. Doctors Brush, Wylie, and Beninson[4] have published a paper subsequent to my own.

The work at the Cleveland Clinic has been largely an extension of the experience gained by these workers in addition to incorporating the teachings of Dr. David V. Habif of the Department of Surgery, Columbia Presbyterian Medical Center, New York, in regard to the role of infection in lymphedema of the arm after radical mastectomy.

December 30, 1959

RICHARD C. BRITTON, M.D.
Department of Vascular Surgery

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